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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/550,220

10/23/2006

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EXAMINER

GAMETT, DANIEL C

ART UNIT

PAPER NUMBER

1647

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DELIVERY MODE

12/16/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/550,220	Applicant(s) BEACHY ET AL.	
	Examiner DANIEL C. GAMETT	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-58 is/are pending in the application.
- 4a) Of the above claim(s) 28-49 and 53-58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-32, 37 and 50-52 is/are rejected.
- 7) ☒ Claim(s) 9 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 September 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/26/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election without traverse of 1-32, 37, and 50-52 in the reply filed on 10/28/2008 is acknowledged.
2. Claims 33-36, 28-49, and 53-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/28/2008.
3. Claims 1-32, 37, and 50-52 are under examination.

Claim Objections

4. Claim 9 is objected to because of the following informalities: The expression "population of stem *cell or differentiate* into a substantially uniform population" does not make sense and appears to be a typographical error. For purposes of examination, the claim is interpreted as "population of stem *cells differentiate* into a substantially uniform population". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1-32, 37, and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing differentiation of an embryonic neural stem cell into a neuron, comprising contacting a stem cell with a Hedgehog protein and β -

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cyclodextrin (β -CD), does not reasonably provide enablement for any method for any that produces a substantially uniform population of differentiated neurons, wherein the cell contacted with a Hedgehog protein and β -cyclodextrin is any cell other than an embryonic neural stem cell, or for any method that produces a substantially uniform population of cells other than floor plate or motor neurons, or the active protein is any other than a Hedgehog protein, or the resultant substantially uniform population is uniformly any particular type of neuron other than motor neuron. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring “ingenuity beyond that to be expected of one of ordinary skill in the art” (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that “... where a statement is, on its face, contrary to generally accepted scientific principles”, a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Among

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the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention and the breadth of the claim: The claims are drawn to methods for inducing differentiation of a stem cell into a neuron, comprising contacting any stem cell or stem cell population with a Hedgehog protein and β -cyclodextrin (β CD) under conditions sufficient to decrease sterol concentration in the cell.

8. *The state of the prior art and the predictability or lack thereof in the art:* Shh is known to be primarily involved in morphogenic and neuroinductive activities during embryonic development (see [0062] in the specification as filed). Pluripotent embryonic stem cells can be directed to become Shh-responsive neural progenitors by the action of retinoic acid (Wichterle *et al.*, Cell Volume 110, Issue 3, 9 August 2002, Pages 385-397). Long after the instant application was filed, it remained unclear whether Shh regulates adult stem cell lineages in a manner equivalent embryonic and fetal stages, or even which cells respond to Shh signaling in adult stem cell niches (Palma *et al.*, Development, 2005 Jan;132(2):335-344 (see Abstract)). Palma *et al.* found that Shh by acts as a mitogen to promote proliferation, not differentiation, of stem cells in adult mouse brain (see Abstract).

9. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The neuronal inducing effects of Hedgehog protein and β -cyclodextrin were demonstrated only with neural plate and epidermal ectoderm

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dissected from stage 9-10 chick embryos, cultured in collagen, and induced with purified Sonic Hh N-terminal autoproteolytic peptide, ShhN. Methyl- β -cyclodextrin was added to the chick explant cultures 4 h after induction with ShhN was initiated ([0106] in the specification as filed; [0110] in the published application). A substantially uniform expression of ISL1, an intermediate-threshold response indicative of motor-neuron fate, was observed with 30 nM ShhN followed by 400 μ M cyclodextrin. All other treatments resulted in expression of floor plate marker NNF β 3; “floor plate” is not a specific neuronal type, but is a source of many cell types ([0114] in the specification as filed). The specification does not show any conditions wherein β -CD is sufficient to positively effect TGF β signaling, or that BMP ever produces a substantially uniform population of neurons, as recited in claims 20-23. β -CD does not seem to alter the effect of BMP ([0115] in the specification as filed).

10. *The quantity of experimentation needed:* It is not certain that uniform neuronal differentiation of the full range of stem cells encompassed by the claims can be achieved regardless of how much experimentation a skilled artisan might be willing to perform. Further, as stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), “If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.”

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Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647